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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,069	04/10/2001	Marschall S. Runge	D6179CIP	8710

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,069	RUNGE ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed January 16, 2002. Currently, claims 1-13 are pending.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 11-13 are indefinite over the recitation "said treatment" in step (b) of Claim 11 because "said treatment" lacks proper antecedent basis. The claim does not refer to a treatment. The claim discusses administer a drug to an individual, but not a treatment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

4. Claims 1-2, 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997).

Yan et al. (herein referred to as Yan) teaches in vivo evidence of the relationship of reactive oxygen species and mitochondrial DNA damage in atherosclerosis. Specifically, Yan teaches assaying both diseased and normal human aortic tissues for DNA damage using a gene-specific quantitative PCR assay (limitations of Claim 2). Yan teaches designing primers to amplify a fragment of the human mitochondrial genome and a nuclear fragment within the beta-globin gene. Fresh surgical specimens of normal and atherosclerotic human aorta were immediately frozen in liquid nitrogen. Yan reports that mtDNA damage detected in atherosclerotic tissue was 2 to 5 fold

higher than that of human aortic samples without evidence of atherosclerosis (limitations of Claim 1, 2, 5). The evidence suggest that the average DNA lesion frequency in the mitochondrial genome was approximately four times higher than that in the nuclear B-globin gene (limitations of Claim 6, 7, 8, 10). Yan teaches that the data suggest that oxidative mtDNA damage may play a role in atherosclerotic lesion development.

5. Claims 1-2, 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Corral-Debrinski et al (Mutation Research, Vol. 275, pages 169-180, 1992).

Corral-Debrinski et al. (herein referred to as Corral-Debrinski) teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease. Corral-Debrinski teaches sampling cardiac tissue and estimating mtDNA damage using PCR (page 172, col. 1-2)(limitations of Claim 2). Table 1 and Table 2 illustrate control and atherosclerotic heart disease characteristics respectively for mtDNA deletion. Figure 2 illustrates the mtDNA deletion vs. age for control hearts and chronic coronary atherosclerotic hearts. It is evident that mtDNA damage occurs at a higher percentage in coronary atherosclerotic hearts than in control hearts.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) or Corral-Debrinski et al (Mutation Research, Vol. 275, pages 169-180, 1992) and further in view of Herrnstadt et al. (US Pat. 6,218,117, April 2001).

Yan et al. (herein referred to as Yan) teaches in vivo evidence of the relationship of reactive oxygen species and mitochondrial DNA damage in atherosclerosis. Specifically, Yan teaches assaying both diseased and normal human aortic tissues for DNA damage using a gene-specific quantitative PCR assay (limitations of Claim 2). Yan teaches designing primers to amplify a fragment of the human mitochondrial genome and a nuclear fragment within the beta-globin gene. Fresh surgical specimens of normal and atherosclerotic human aorta were immediately frozen in liquid nitrogen. Yan reports that mtDNA damage detected in atherosclerotic tissue was 2 to 5 fold higher than that of human aortic samples without evidence of atherosclerosis

(limitations of Claim 1, 2, 5). The evidence suggest that the average DNA lesion frequency in the mitochondrial genome was approximately four times higher than that in the nuclear B-globin gene (limitations of Claim 6, 7, 8, 10). Yan teaches that the data suggest that oxidative mtDNA damage may play a role in atherosclerotic lesion development.

Corral-Debrinski et al. (herein referred to as Corral-Debrinski) teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease. Corral-Debrinski teaches sampling cardiac tissue and estimating mtDNA damage using PCR (page 172, col. 1-2)(limitations of Claim 2). Table 1 and Table 2 illustrate control and atherosclerotic heart disease characteristics respectively for mtDNA deletion. Figure 2 illustrates the mtDNA deletion vs. age for control hearts and chronic coronary atherosclerotic hearts. It is evident that mtDNA damage occurs at a higher percentage in coronary atherosclerotic hearts than in control hearts.

Neither Yan nor Corral-Debrinski teaches methods of determining the efficacy of a drug by administering a drug to a sample and determining the level of mitochondrial DNA damage.

However, Herrnstadt teaches methods for identifying agents for treating a disease associated with altered mitochondrial function. Herrnstadt teaches that biological samples may be treated by heating in water to lyse cells contained in the sample and then extracting cellular DNA from lysed cells using an aqueous DNA extraction procedure. Specifically, Herrnstadt teaches that methods of comparing the

ration from a sample obtained before contacting a biological source with a candidate agent obtained after contacting the biological source with the agent.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of detecting atherosclerotic state of an individual by determining mtDNA damage with the improved method of determining whether drugs are efficient in reducing the risk of atherosclerosis in an individual. The art clearly provides that mtDNA damage is associated with atherosclerosis, see Yan and Corral-Debrinski. Therefore, once this is known in the art, the ordinary artisan would be motivated to determine possible treatments for such risks. Thus, the ordinary artisan would look to other methods of determining whether an agent is effective for reducing risk given the teachings in the art. Herrnstadt teaches that agents may be determined by comparing the mitochondrial DNA prior and following treatment. Therefore, the ordinary artisan would have been motivated to have evaluated candidate agents, drugs, for the efficacy in treating a well known problem.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-13 of U.S. Patent No. 6,322,974.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claims 1-13 of the instant application is generic to all that is recited in Claims 1-13 of U.S. Patent No. 6,322,974. That is, Claims 1-13 of U.S. Patent No. 6,322,974 falls entirely within the scope of Claims 1-13, or in other words, Claim 1-13 are anticipated by Claims 1-13 of U.S. Patent No. 6,322,974. Here, claims 1-13 of U.S. Patent No. 6,322,974 recites methods of evaluating the atherosclerotic state of a patient using a blood sample; measuring the amount of oxidative stress using a blood sample and a method of determining the efficacy of a drug to reduce the risk of atherosclerosis in a patient using a blood sample. The instant claims are drawn generically to tissue. Therefore, the instant claims embody the patented claims.

Conclusion

9. No claims allowable over the art.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Ferrari (J. of Cardiovascular Pharmacology, Vol. 28, Suppl. 1, pages S1-S10, 1996). Ferrari teaches mitochondrial DNA deletion rose to a maximum of 0.007% in normal hearts and increased to between 0.02% and 0.85% in CAD patients.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
November 18, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600